

U.S. DEPARTMENT OF COMMERCE, PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER  
33891R005

U.S. APPLICATION NO. (if known,  
see 37 CFR 1.55)  
10/009559

INTERNATIONAL APPLICATION NO.  
PCT/SE00/01267

INTERNATIONAL FILING DATE  
15 June 2000

PRIORITY DATE CLAIMED  
15 June 1999

TITLE OF INVENTION  
RECEPTOR AGONISTS AND ANTAGONISTS

APPLICANT(S) FOR DO/EO/US --- Staffan Skogvall

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(I).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))  
a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau) b. ☒ has been transmitted by the International Bureau (see Form 308) c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2))
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))  
a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau)  
b. ☐ have been transmitted by the International Bureau.  
c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.  
d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98. (w/ copy of PTO-1449 and each reference cited therein and Int'l Search Rept)
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.  
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:  
a) International Search Report (PCT/ISA/210) (original "A2" version and revised "A3" version),  
b) International Preliminary Examination Report (PCT/IPEA/409) including the amended claim set to be prosecuted;  
c) PCT Publ. WO 00/76500  
d) Formal Drawing Set (included with international application)  
e) Form PCT/IB/308  
f) Form PCT/IPEA/402  
g) PCT Request (Form PCT/RO/101)

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

10/009559  
JG 13 Rec PCT/PTO 14 DEC 2001

U.S. APPLICATION NO. (if known, see  
37 CFR 1.5)

17. ☒ The following fees are submitted:

CALCULATION

PTO USE ONLY

**Basic National Fee (37 CFR 1.492(a)(1)-(5)):**

Search Report has been prepared by the EPO or JPO ..... \$890.00  
International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... \$670.00  
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee  
paid to USPTO (37 CFR 1.445(a)(2)) ..... \$760.00  
Neither international preliminary examination fee (37 CFR 1.482) nor  
international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$970.00  
International preliminary examination fee paid to USPTO (37 CFR 1.482)  
and all claims satisfied provisions of PCT Article 33(2)-(4) ..... \$96.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

\$970.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest  
claimed priority date (37 CFR 1.495(e)).

\$ -

Claims	Number Filed	Number Extra	Rate		
Total Claims	20 - 20 =	0	x \$18.00	\$ .00	
Independent Claims	3 - 3 =	0	x \$8400	\$ .00	
Multiple dependent claim(s) (if applicable)			+ \$280.00	280.00	
TOTAL OF ABOVE CALCULATIONS =				\$1250.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)				\$ 625.00	
SUBTOTAL =				\$ 625.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$ -	
TOTAL NATIONAL FEE =				\$625.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property.				\$ .00	
TOTAL FEES ENCLOSED =				\$625.00	
				Amount to be refunded	\$
				charged	\$

- a. ☒ A check in the amount of \$ 625.00 to cover the above fees is enclosed.  
b. ☐ Please charge my Deposit Account No. 02-4300 in the amount of \$          to cover the above fees. A duplicate copy of this sheet is enclosed.  
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required with respect to any deficiency in the above noted "Basic National Fee", or credit any overpayment to Deposit Account No. 02-4300.

**NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.**

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NAME REGISTRATION NO

Date: December 14, 2001

1/pts

# RECEPTOR AGONISTS AND ANTAGONISTS

## Field of the Invention

The present invention relates to a compound having agonist activity to the 5-HT<sub>1</sub> receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered. The present invention also relates to a compound having antagonist activity to the 5-HT<sub>2</sub> receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compound is administered.

## Background of the Invention

Receptors of the 5-HT (serotonin; 3-( $\beta$ -aminoethyl)-5-hydroxyindole) type are well known and occur throughout the body, e.g. in the airways, and their relevance has mainly been reported in conjunction with treatment of CNS, muscle and gastric disorders, as disclosed in e.g. WO 98/18458 and US 5 246 935. In such treatments, compounds having agonist activity to a 5-HT<sub>1</sub> type receptor are often used. As examples of other 5-HT receptors, mention can be made of receptors of the 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>5</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub> type. For a recent review of 5-HT receptors, see Gerhardt, C.C., van Heerikhuizen, H., Eur. J. Pharm., 334, 1-23 (1997), which is incorporated herein by reference.

A review of typical agonists and antagonists of various 5-HT receptors is disclosed in R.A. Glennon, Neuroscience and Biobehavioral Reviews, 14, 35-47 (1990), the whole content of which is incorporated herein by reference.



treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having agonist activity to the 5-HT<sub>4</sub> receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

The present invention also relates, in another aspect, to a compound having antagonist activity to the 5-HT<sub>3</sub> receptor for use as a medicament. In another aspect it relates to use of said compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a human or animal body, wherein the medicament is intended for treatment of disorders involving bronchocontraction, such as asthma.

In a preferred embodiment, the invention relates to the use of a compound having antagonist activity to a 5-HT<sub>2a</sub> receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

Said bronchocontraction may also occur in conjunction with such disorders as e.g. emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions, including schizophrenia.

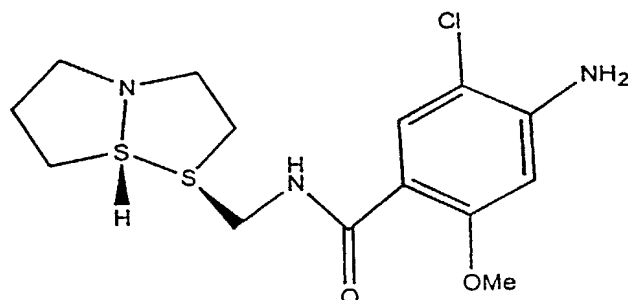
The present invention also relates to the use of a compound having antagonist activity to a 5-HT<sub>3</sub> receptor in combination with a compound having agonist activity to the 5-HT<sub>4</sub> receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders in-

volving bronchocontraction. In a preferred embodiment said compound having agonist activity is serotonin or a derivative thereof having agonist activity to the 5-HT<sub>4</sub> receptor. This combination of the 5-HT<sub>3</sub> receptor antagonist and the agonist increases the beneficial effect of serotonin, particularly in the presence of a serotonin uptake inhibitor (SRI). Further, the compounds having agonist activity to the 5-HT<sub>4</sub> receptor to be used according to the present invention are also useful in the present combination embodiment. In particular, said medication is intended for treatment of asthma and disorders related thereto.

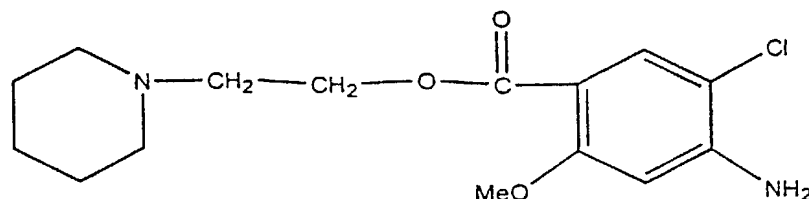
According to the present invention several known substances are able to stimulate the 5-HT<sub>4</sub> receptor, without activating the contracting 5-HT<sub>3</sub> receptor, thereby, surprisingly, generating a relaxing effect on the bronchocontraction. Such agonist compounds are selected from the group comprising the substances SC 53116, ML 10302, RS 67506 and BIMU 8, which are defined below, as well as the more unspecific 5-carboxamidotryptamine, and derivatives and pharmaceutically acceptable salts thereof having the same or essentially the same relaxation effect.

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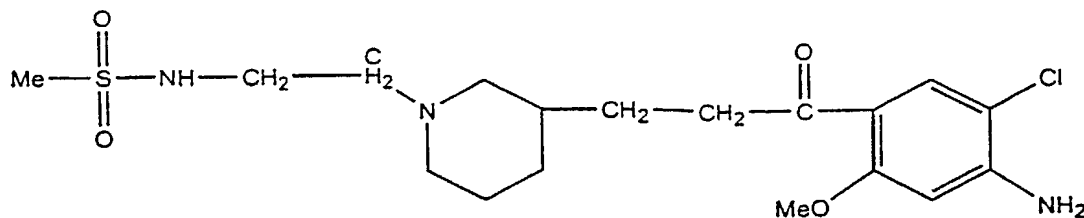
The invention also relates to the use of one or more of the above-mentioned agonist compounds: SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural formula:



ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidiny)ethylester, having the structural formula:

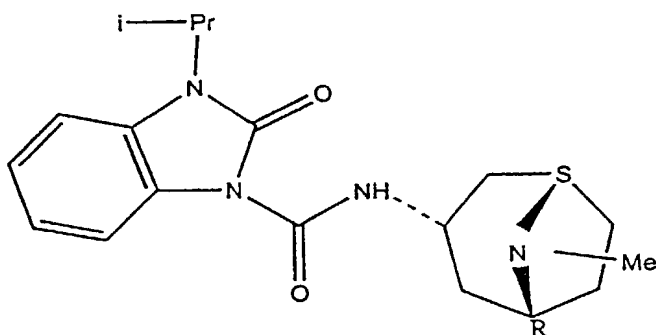


RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidiny]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:



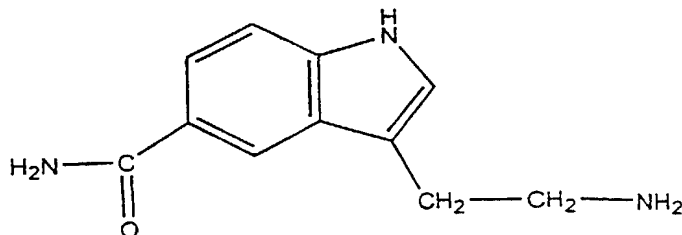
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BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



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5-carboxamidotryptamine (5-CT), having the structural formula:



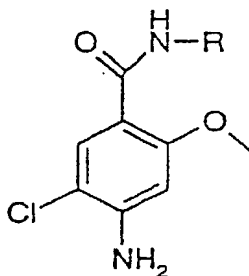
10

ADR932, BIMU 1, BRL 20627, BRL 24682, BRL 24924, Cinitaprid, Cisapride, DAU 6215, DAU 6236, 5-HT, 5-hydroxy-N,N-dimethyltryptamin, 3-Me-8-OH-DPAT, ML-1035, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877 (prucalopride), Renzapride, RS 17017, RS 23597-190, RS 56532, RS 57639, RS 67333, RS 67532, RU 28253, SB 204070, SB 205149, SC-52491, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, Y-34959, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac (SDZ HTF919; tegaserod) and derivatives and pharmaceutically acceptable



salts thereof having essentially the same relaxing effect, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, wherein said agonist has the capacity of reducing the bronchocontraction by at least 30%, preferably at least 60%, most preferably at least 90%.

Most of the different 5-HT<sub>4</sub> agonists can be divided in certain groups, wherein each group contains a common structural element. The largest group, and also the basis for several others, are the benzamides. They all contain the structural element 4-amino-5-chloro-2-methoxy benzamide and are further developments of the first 5-HT<sub>4</sub> agonist, metoclopramide.



These compounds are also potent 5-HT<sub>3</sub>-antagonists:

- 3-(4-Allylpiperazin-1-yl)-2-quinoxalinecarbonitrile
- 5-[(Dimethylamino)methyl]-3-(1-methyl-1H-indol-3-yl)-1,2,4-oxadizole
- 3-(1-Piperazinyl)-2-quinoxalinecarbonitrile
- Granisetron
- RS-25259-197
- SEC-579, Mirisetron
- SC-52491
- KB-6933
- BRL 46470, Ricasetron
- Lerisetron
- KAE-393/YM-114
- AS-5370
- DAT-582
- N-3256
- SDZ 214-322
- KF-20170
- Lurosetron
- Galdanetron
- ONO-3051
- CP-93318
- Batanopride
- GR 67330
- SDZ 206-830
- QICS 205-930
- BRL 24682
- LY 258-458
- Zacopride, S(-)Zacopride, R(+)Zacopride
- RP 62203
- SDZ 206-792
- BRL 47204
- SDZ 210-204
- LY-211-000
- MCPP
- MK 212
- Mianserin
- SDZ 210-205

- Bufotenine
- Pitozifen
- Indalpine
- Cizapride
- Cyproheptadine
- 2-Methyl-5HT
- Amitriptyline
- LY 278-989
- Imipramine
- Phenylbiguanide
- TFMPP
- 5,7-DHT
- RU 24969
- Ritanserin
- NAN-190
- Mepyramine
- Metergoline
- Methysergide

These compounds are also potent 5-HT<sub>4</sub>-agonists:

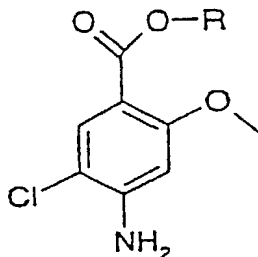
- Bufotenine
- 5-MeO-N,N,DMT
- GR 113,808
- $\alpha$ -Metyl-5HT

Another common feature is a basic nitrogen in a side chain from the amide nitrogen. This basic nitrogen is often a part of a sterically locked system. Examples of substances from this group are:

BRL 20627, BRL 24682, BRL 24924, Cisapride, Metoclopramide, ML-1035, Mosapride, R076186, Renzapride, RS 67506, Cinitapride, SB 205149, SC-49518, SC-52491, SC-53116, TKS 159, Y-34959, YM-09151, YM-47813, Zacopride.

Thus, a structure-activity relation study performed indicates that a benzene ring and a basic nitrogen in the same plane as the ring and at a distance of  $8 \pm 1$  Å from the center of the benzene ring is required. The nitrogen should be locked in that position with a view to obtaining selectivity against other 5-HT receptors. A lipophilic group on the basic nitrogen also seems to be important for the agonistic action. Further, a heteroatom having a free electron pair close to the indole nitrogen in tryptamine seems to give a positive effect.

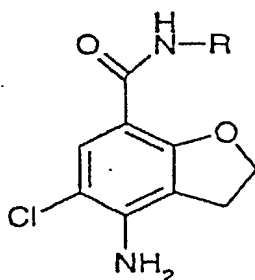
Benzoic acid esthers are modifications of the benzamide theme:



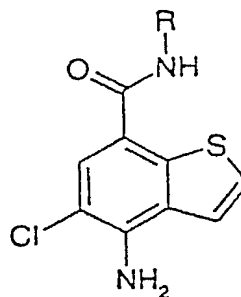
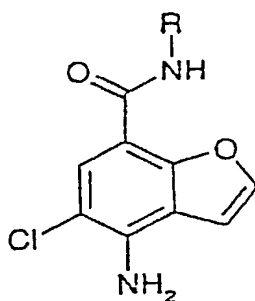
The only difference is that the amide group has been replaced with an esther group. Examples are ML 10302, RS 57639, and SR 59768.

11

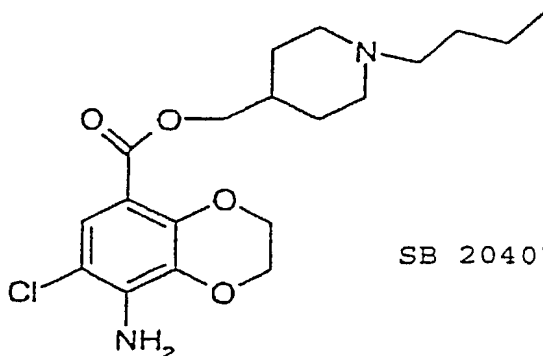
Another variant of the basic theme is to introduce the methoxy group into a ring, thereby arriving at a 2,3-dihydro-bensofuran-7-karboxamide group. Examples are ADR 932, Prucalopride (=R 093877); and SK-951.



Benzofuranes and benzothiophenes are also contemplated,



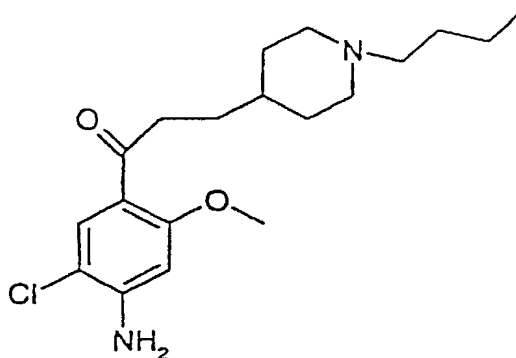
as well as the benzodioxan



SB 204070

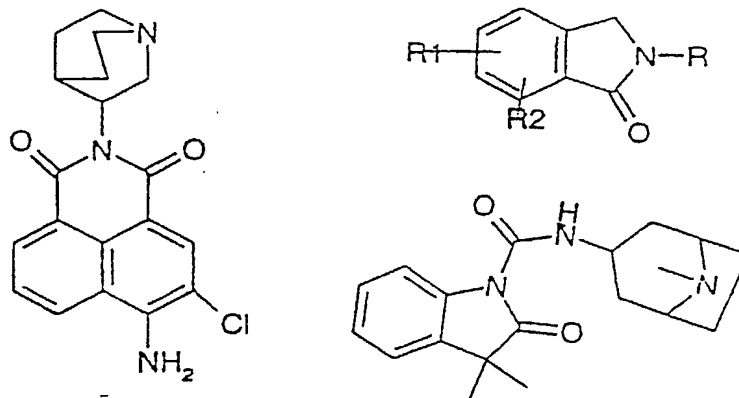
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Still another variant is based on the discovery that the benzoic acid antagonist RS 23597 (an ester) was transformed to an agonist if it was converted to a ketone



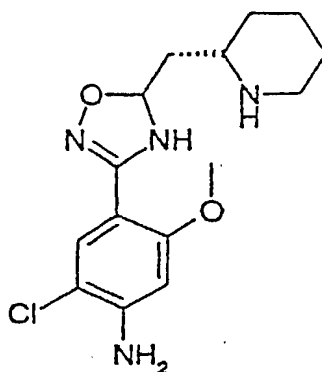
, e.g. RS 67333 and RS 17017.

The basic concept also applies for naphtalimides, e.g. RS 56532.



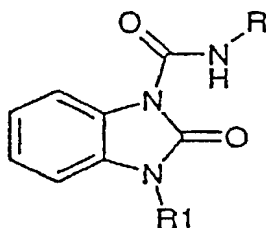
Benzindolones are also contemplated

The amide function may also be replaced with an oxadiazol ring.



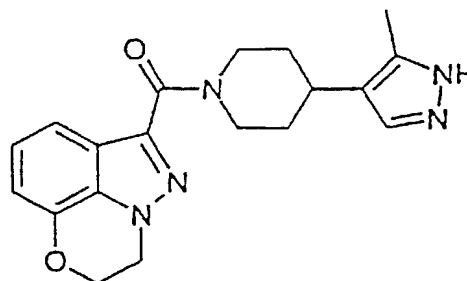
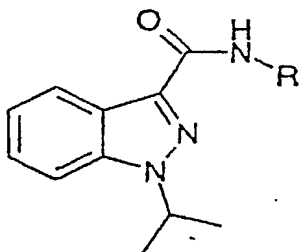
, e.g. YM-53389

## Benzimidazolone-1-carboxamides



, e.g. BIMU 1, BIMU 8, DAU 6215, and DAU 6236, are also contemplated.

The carboamides

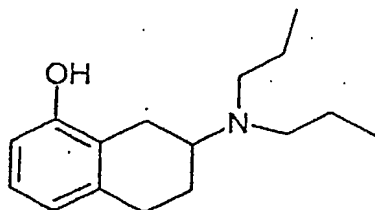


are also contemplated.

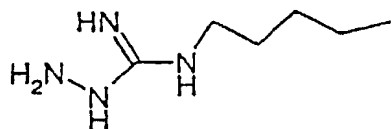
Some indols are also useful as 5-HT<sub>4</sub> agonists, e.g. 5-methoxytryptamine, 2-methylserotonine, and 5-hydroxy-N,N-di-methyltryptamine.

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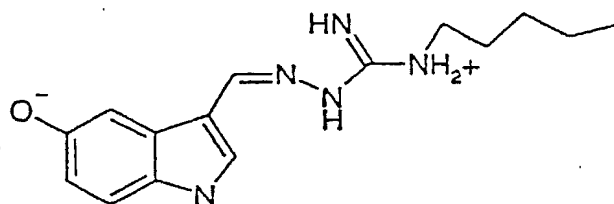
Other tested substances useful as 5-HT<sub>4</sub> agonists according to the present invention are



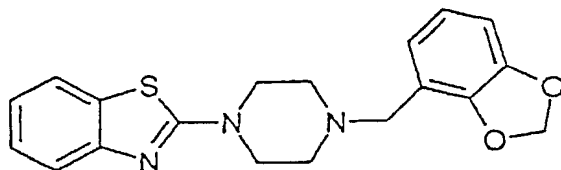
SDZ 216-454



Zelmac=SDZ HTF 919



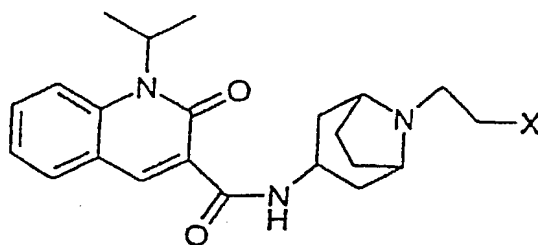
VB20B7



It should be noted that many of these substances may be quaternized on the nitrogen in the side chain without losing the activity.

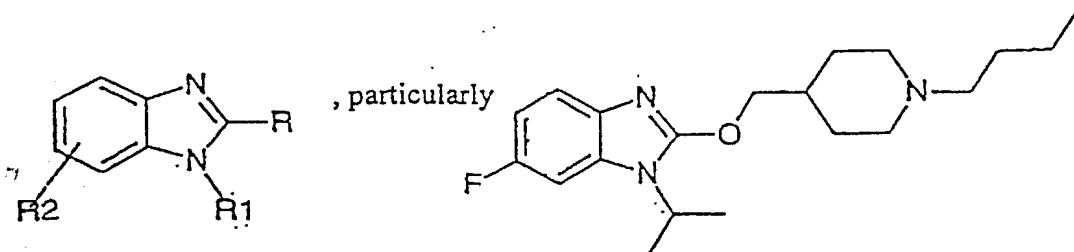
The most active agonist at present seems to be Zelmac.

Benzokinolinones

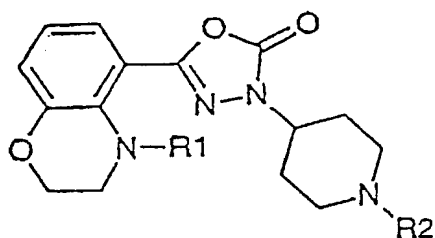




Further 5-HT<sub>4</sub> agonist structures useful according to the present invention



2-piperidinmethylethers  
of bensimidazol



oxadiazalon based  
substance

Arylcarbamate derivatives of 1-piperidineethanol  
4-amino-5-chloro-2-methoxybenzoic acid esters,  
e.g. ML10302, RS 57639 and SR59768

4-amino-5-chloro-2-methoxy-N-((2S,4S)-  
1-ethyl-2-hydroxymethyl-4-  
pyrrolidinyl)benzamide, e.g. TKS159

thiophene carboxamide derivatives 3 (a-j)

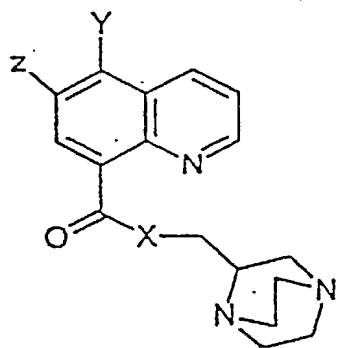
5. Azabicyclo(x.y.z) derivatives

2-piperazinylbenzoxazole derivatives

2-piperazinylbenzothiazole derivatives, e.g. VB20B7

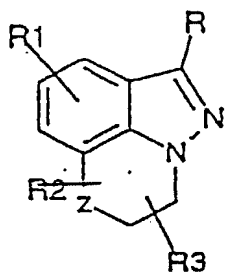
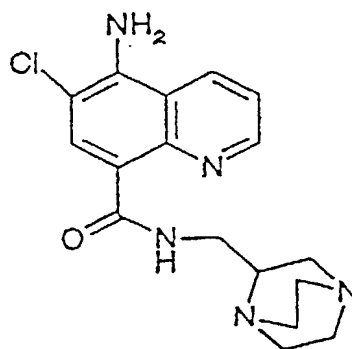
clebopride

Sandoz compound 1b

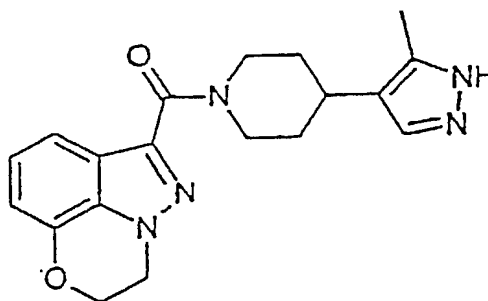


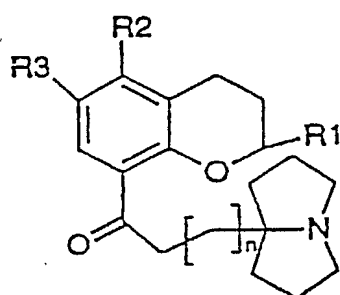
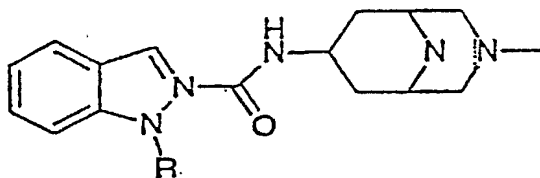
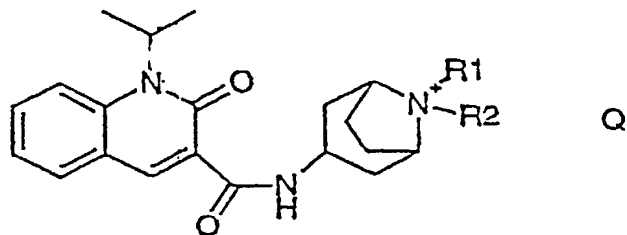
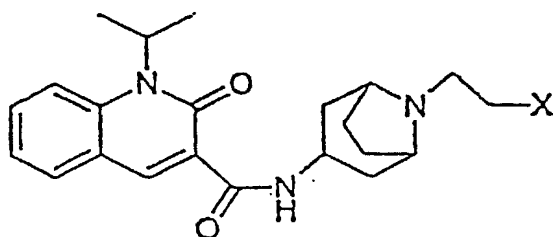
kinolines

, particularly

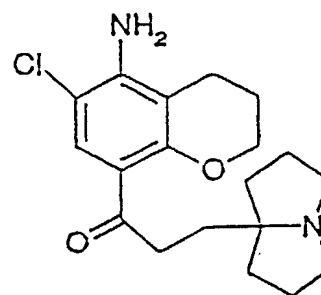


, particularly

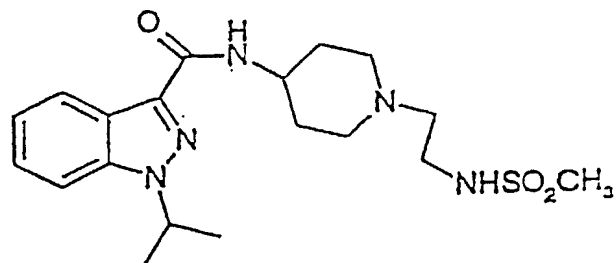
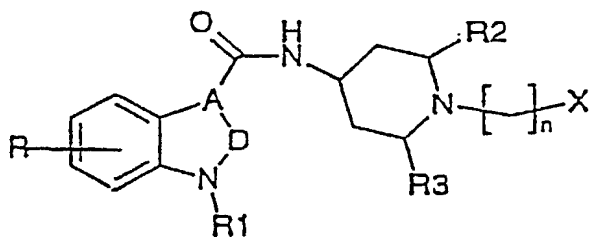




, particularly



bensopyranes



The most preferred 5-HT<sub>4</sub> receptor agonist is RS 67333.

According to the present invention several known antagonist compounds are, surprisingly, able to influence the 5-HT<sub>3</sub> receptor, thereby generating a contraction reducing effect, i.e. a relaxation effect, and are selected from a group comprising 4-Ph-N-Me-quipazine, ADR-851, ADR-882, Alosetron, Anpirtoline, Azasetron (=Y 25130), BIMU 1, BMY 33462, BRL 24924, BRL 43694, BRL 46470 A, CF 109203 (=BIM), Chlorpromazine, Cilansetron (=KC 9946), Cisapride, Clozapine, Cyameazine, DAT-582 (=R)AS-5370), Diltiazem, Dolasetron (=MDL 74156), Dolasetron mesilat (=MDL 73147 EF), Droperidol, FK 1052, Fluphenazone, Galanolactone, GK 128, GR 38032 F, GR 65630, Gramisetron (=Kytril=BRL 43694), GR-H, GYK1-48903, ICI 169369, ICS 205-930, Ifenprodil, Iodophenpropit, Itasetron (=DAU 6215), KB-6922, KB-R 6933, KF 17643, KF 18259, L-683877, Litoxetine, LY 278584, McNeil-A-343, MDL 72222, MDL 72699, Metoclopramid, Mirtazapine, Mosapride, N-3389, N-methylquipazin, Ondansetron (=GR 38032 F), Palonosetron, Pancopride, Perphenazine, Prochlorperazine (=Stemetil), Quipazine, QX 222, (R)-zacopride, Ramosetron (=YM 060), Renzapride, RG 12915, RS-25259, RS 42358-197, RS 56532, RS-056812-198, RS-25259-197, RS-56812, S-apomorfin, SC-53116, SDZ 216-525, SDZ 322, SN-307, Talipexole, Thioperamide, TMB 8, Trifluoperazine, Trimebutine, Tropisetron (=ICS 205-930=Rifenserin), VA 21 B 7, Way 100289, WAY-100579, WAY-SEC-579, Y 2513, YM 114 (=KAE-393), Zatose-  
tron (=LY 277359) and pharmaceutically acceptable salts thereof having the same or essentially the same contraction reducing effect.

The present invention also relates to the use of one or more of the above-mentioned 5-HT<sub>3</sub> antagonist compounds and to derivatives and pharmaceutically acceptable salts thereof having essentially the same contraction reducing effect, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving

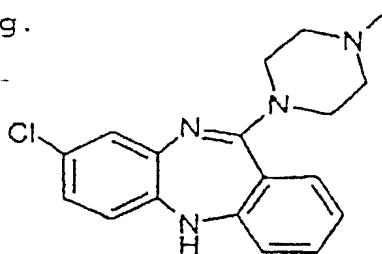
bronchocontraction, wherein said antagonist has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%.

5       The 5-HT<sub>3</sub> receptor is a ligand modulated ion channel. The known anxiety repressing benzodiazepines influence not only 5-HT<sub>3</sub> but also several other receptors for different neurotransmitters. Several potent specific 5-HT<sub>3</sub> antagonists exist today, of which ondansetron, tropisetron, granisetron, and dolasetron are commercial  
10       pharmaceuticals, however, not against disorders involving bronchocontraction.

      Some of the 5-HT<sub>3</sub> receptor antagonists are at the same time 5-HT<sub>4</sub> receptor agonists. However, for a substance to be active as a 5-HT<sub>3</sub> receptor antagonist, the  
15       distance from the aromatic center to the basic nitrogen should be about 7,5 Å and no large substituents are tolerated on the basic nitrogen. In contrast, for 5-HT<sub>4</sub> receptor agonists the corresponding distance is about 8 Å,  
20       and a large lipophilic group may be bound to the basic nitrogen, thereby obtaining a better binding to 5-HT<sub>4</sub>.

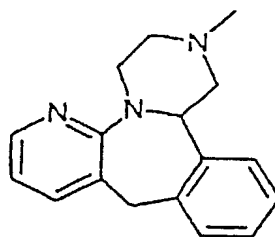
      The 5-HT<sub>3</sub> antagonist may be divided in certain classes with the basis on the chemical structure. Some are unspecific, e.g.

25



30       benzazepines, e.g. mirtazapine

35

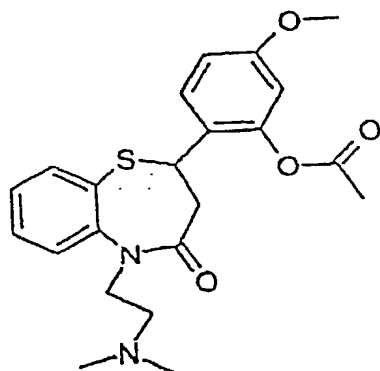


benzthiazepines, e.g. diltiazem

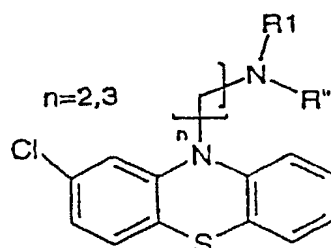
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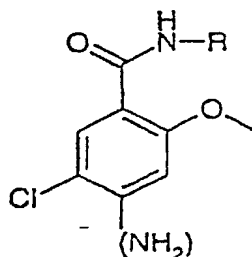


10 and fentiazines



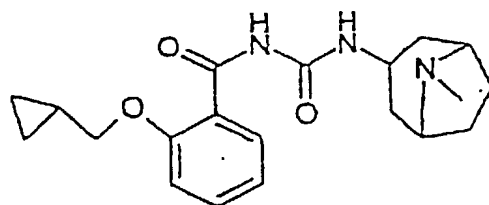
, e.g. perphenazine, chlorpromazine, stemetil

Some are 5-HT<sub>4</sub> agonists, e.g. benzamides



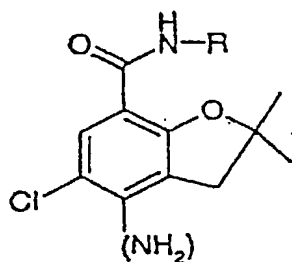
(cisapride, zacopride,  
mosapride, metoclopra-  
nide, pancropride,  
BRL 24924, BMY 33462)

and



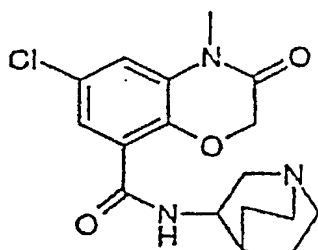
WAY 100289

2,3-dihydro-benzofuran-7-carboxamides



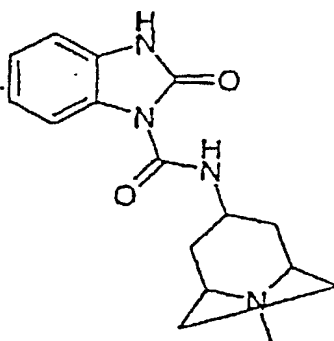
(e.g. zatosetron=LY 277359, ADR 851)

10  
1,4-benzoxazin-8-carboxamides



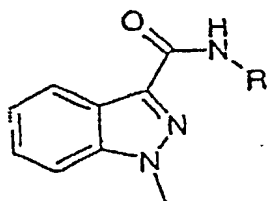
, e.g. azasetron (=Y25130)

20  
benzimidazolones



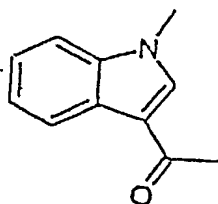
, e.g. itasetron (=DAU 6215)

indazol-3-carboxamides

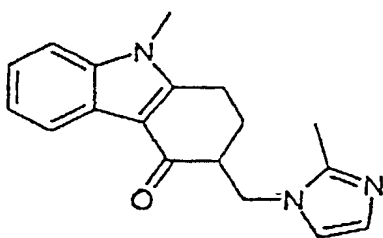


, e.g. N 3389, LY 278584, DAT 582

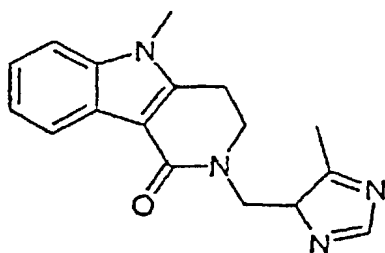
The latter group reminds most of the specific 5-HT<sub>3</sub> antagonists, which after contains the group



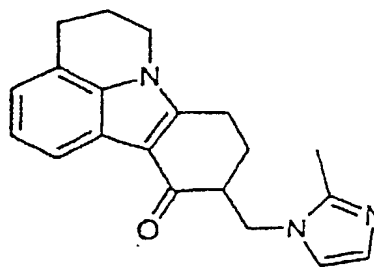
in different forms, such as



ondansetron



alosetron

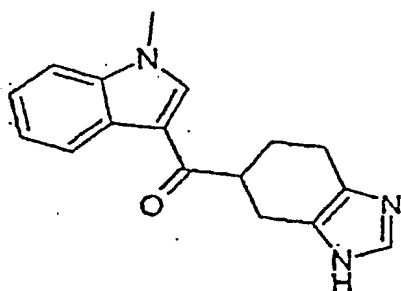


cilansetron

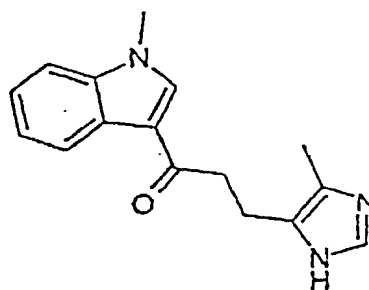
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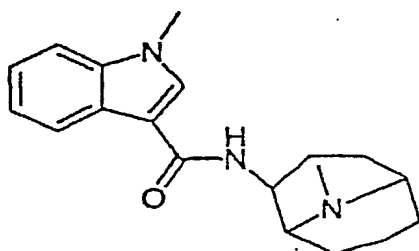
PCT/SE00/01267



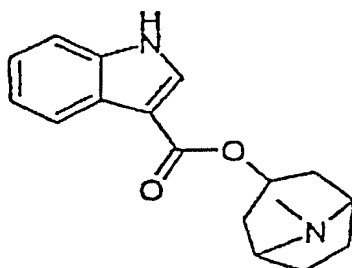
ramosetron



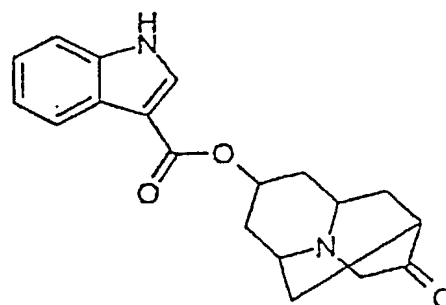
GR 65630



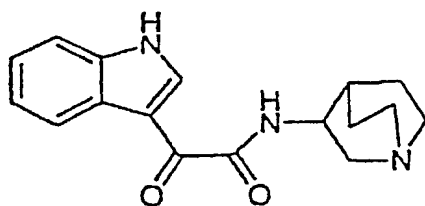
granisetron



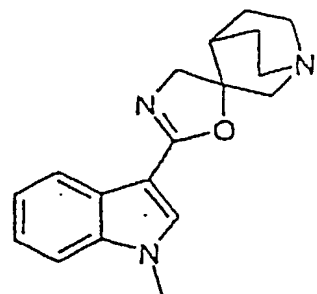
tropisetron



dolasetron



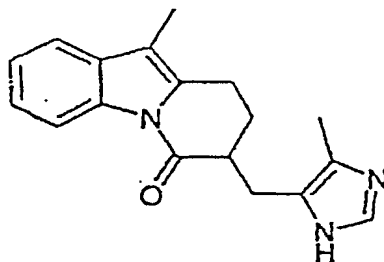
RS 56812



L 683877

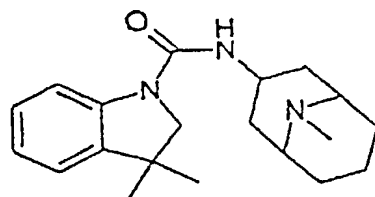


In one group of substances the structure has been inverted and the carbonyl group has been placed on the indoline nitrogen



FK 1052

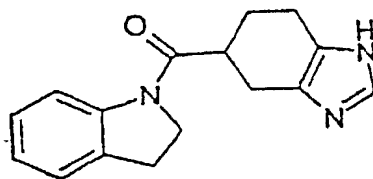
This substance is unique by being an antagonist against both 5-HT<sub>3</sub> and 5-HT<sub>4</sub>.



BRL 46470 A

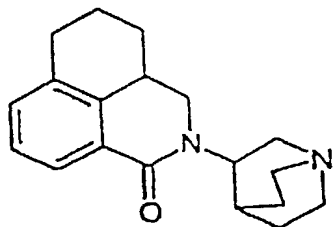
BRL 46470A binds to two different positions of the receptor.

A further development is the so-called bisindoles

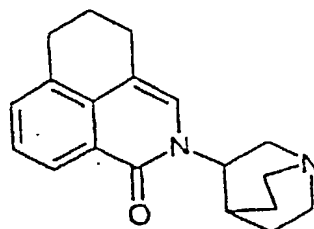


YM 114

Another group is the isoquinoline-1-ones

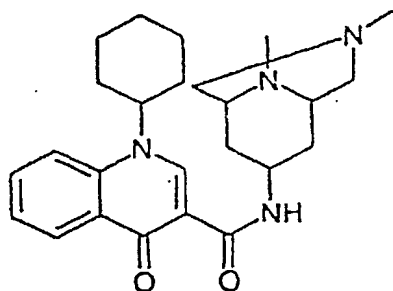


palonosetron (=RS 25259-197)

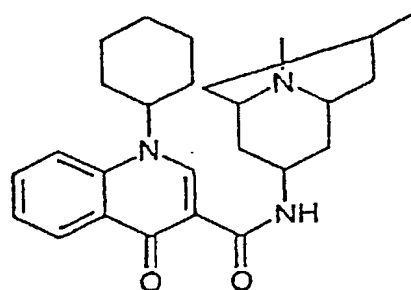


RS 42358-197

and the quinoline-3-carboxamides

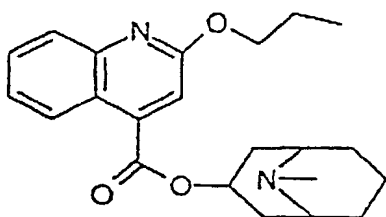


WAY-SEC 579

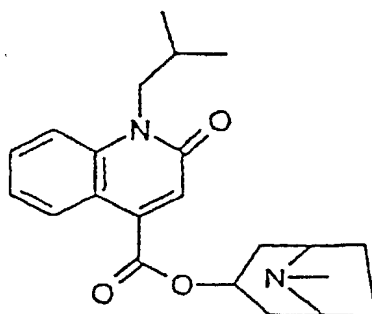


Mirisetron (=WAY 100579)

Also the quinoline-4-carboxylates are active antagonists

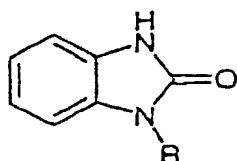


, e.g. KF 17643



, e.g. KF 18259

Other compounds are benzimidazolones



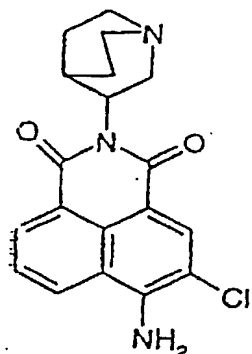
e.g. droperidol (neurolidol, etc.), itasetron (DAU6215),

WO 00/76500

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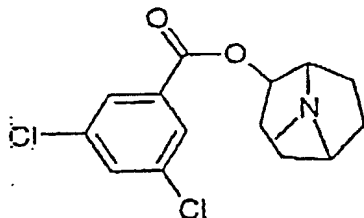
and the naphthimides



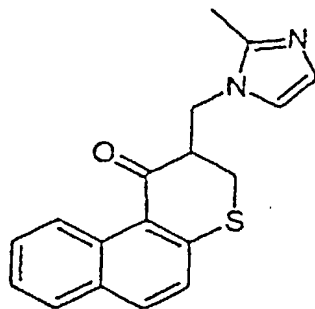
RS 56532

, e.g. RS 56532

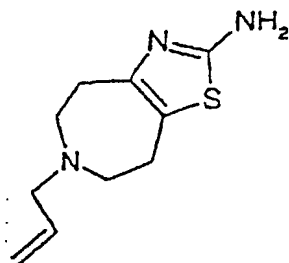
A unique single structure is MDL 72222, which also is a specific 5-HT<sub>3</sub> antagonist



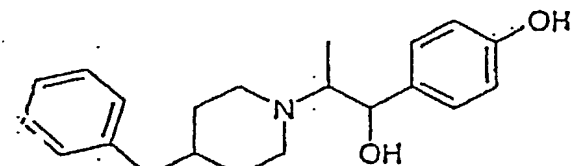
Other specific structures are



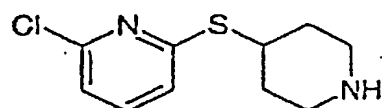
GK 128



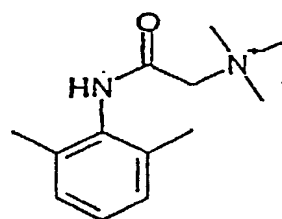
Talipexole



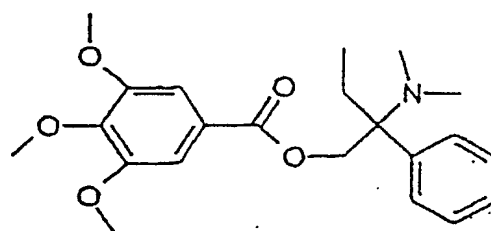
Ifenprodil



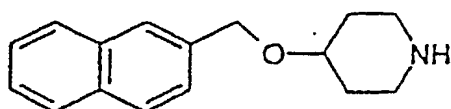
Anpirtoline



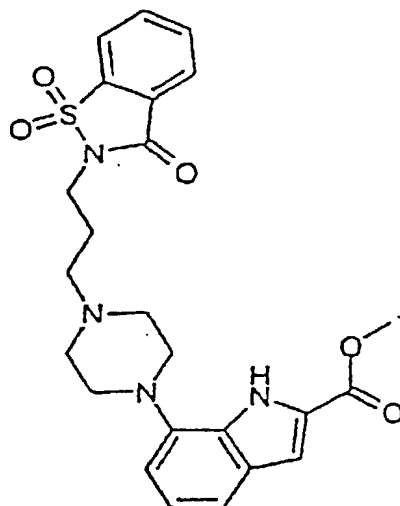
QX 222



Trimebutine

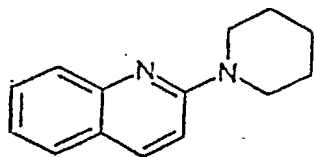


Litoxetine



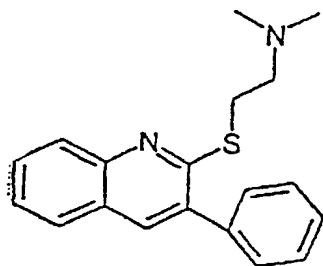
SDZ 216-525

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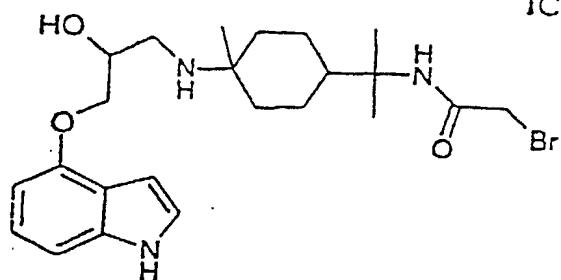
## Quipazine

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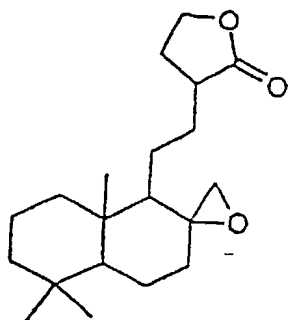
ICI 169369

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BIM

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## Galanolakton

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method relates to treatment of asthma and disorders related thereto.

Further, the present invention relates to a method for treatment of disorders involving bronchocontraction, wherein the above-mentioned combination of agonist(s) and antagonist(s) is administered.

The expression "has the capacity of reducing the pathological bronchocontraction by at least ....%" used throughout the present patent application means that the compound in question reduces the contraction in the airways caused (1) either by the underlying disease (asthma etc) or (2) by the administration of 5-HT or other substances with 5-HT<sub>3</sub>-activating properties. The level of contraction in the airways can, for instance, be determined by spirometric measurements of the Forced Expiratory Volume (FEV<sub>1</sub>), compared to the normal value for healthy people. Alternatively, the expiratory capacity for a patient can be compared to his own FEV<sub>1</sub> during periods of relatively little obstructive problems.

As appears from Fig. 1, the contractile component often manifests itself as a reduction or a complete elimination of the 5-HT induced relaxation, rather than in an increase of force from the control (pre-exposure) level. In the case of "specific" agonists to the 5-HT<sub>4</sub> receptor, this sustained relaxing effect is achieved because the contractile 5-HT<sub>3</sub> receptor is not affected; only the relaxing 5-HT<sub>4</sub> receptor is activated. In the case of antagonists to the 5-HT<sub>3</sub> receptor, this effect is achieved due to direct blocking of the 5-HT<sub>3</sub> receptor, whereby the unspecific agonists to the 5-HT<sub>4</sub> receptor, such as 5-HT, can act without also causing contraction by the 5-HT<sub>3</sub> receptor.

It should be noted that the medicament prepared according to present invention in each embodiment may optionally include two or more of the above outlined compounds.

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### Detailed Description

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the airway smooth muscle, was studied due to a suspicion that defective regulation of the spontaneous tone could be an important cause of the bronchoconstriction observed in asthmatic patients.

5 The examinations of the spontaneous tone were performed in accordance with the methods disclosed in the thesis "*Regulation of spontaneous tone in guinea pig trachea*" by S.Skogvall, Department of Physiological Sciences, Lund University, 1999, which is incorporated  
10 herein by reference. As evidenced by these examinations, the airways normally display a highly regular type of oscillating tone if exposed to physiological conditions, and the oscillating tone can be reversibly affected by administration of various substances. When the epithelium  
15 is removed, the preparations instead display a strong, smooth type of tone.

In short, the animal experiments in said thesis showed that the spontaneous tone to a large degree is controlled by powerful regulating factors released from  
20 neuroepithelial endocrine (NEE) cells.

Later experiments, not included in the thesis, have revealed that one of the regulating factors is serotonin, also called 5-HT, which exerts agonist action on the receptors 5-HT<sub>1</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>5</sub>, 5-HT<sub>6</sub> and 5-HT<sub>7</sub>, as well  
25 as on 5-HT<sub>2</sub> receptors.

Additional experiments have shown that when 1 µM serotonin was added to denuded airway smooth muscle preparations from the guinea-pig displaying a strong, smooth spontaneous tone, the average force level was increased  
30 significantly, i.e. a contraction was observed. A contractile effect of serotonin on airway smooth muscle has been reported in e.g. Skogvall, S., Korsgren, M., Grampp, W., *J. Appl. Phys.*, 86:789-798, 1999. However, when 10 µM of serotonin was added, the spontaneous tone was significantly suppressed to a level of about half the force observed in control (drug-free) conditions. The spontaneous  
35 tone returned to approximately its normal level when the

preparations were again exposed to control conditions. Thus, it has now surprisingly been shown that serotonin brings about contraction of the airways at low concentrations and relaxation at high concentrations, consequently  
5 having a dual effect on the airways.

Furthermore, it has been shown that when the contracting 5-HT<sub>2a</sub> receptor was blocked with ketanserin, the 5-HT, i.e. serotonin, induced almost no contraction, but instead only a significant relaxation. Similar experi-  
10 ments have also been performed on human in vitro preparations, from patients undergoing lobectomy or pneumectomy due to lung cancer. It was found that in this tissue, 5-HT was even more potent in relaxing the airway smooth muscle than in guinea pig. In human tissue, already 1 µM  
15 5-HT induces a significant relaxation of the spontaneous tone.

Human airways are generally considered to display only a weak contraction when exposed to 5-HT. Nevertheless, examinations on spontaneous tone on human in vitro  
20 preparations have shown that 5-HT indeed has a contractile component also in this tissue. However, this contraction takes a longer time to develop than in guinea pig and the contractile effect is seen as a termination of the relaxation, rather than an increase of tone from  
25 the baseline. In guinea pig trachea, the contraction reaches a maximum after approximately 10 min, and this is followed by a considerable reduction of tone. However, human preparations instead induce a maximum relaxing effect after 5-10 min, which disappears gradually during  
30 the following 30-45 min (see Fig 1). The transient nature of the 5-HT relaxation is most likely caused by a simultaneous activation of the fast, relaxing 5-HT<sub>4</sub> receptor, and a slower activation of the contracting receptor, which in human airways surprisingly has been found to be  
35 the 5-HT<sub>3</sub> receptor. This is clear, because activation of the relaxing 5-HT<sub>4</sub> receptor by a substance that lacks 5-HT<sub>3</sub> receptor activating properties (such as RS 67333),

results in a relaxation that is persistent and not transient (see Fig. 1).

It has previously been suggested that 5-HT or 5-HT analogues may be useful in the treatment of bronchoobstructive diseases. In SU 1 701 320 it is suggested that the 5-HT, i.e. serotonin, may be of use as an addition to standard beta2 receptor stimulation. However, from our experiments it seems clear that 5-HT is not effective or useful as the only treatment for e.g. asthmatic disorders, because of the transient relaxing effect by 5-HT (see Fig. 1). If instead, as we propose herein, a 5-HT analogue that lacks the 5-HT<sub>2</sub> activating properties is given, the relaxing effect is persistent, and not transient.

In summary, it has now been discovered that agonist action on the 5-HT<sub>4</sub> receptor results in a relaxing effect, whereas agonist action on 5-HT<sub>3</sub> receptors results in a contractile effect. In conclusion, the dual effect of serotonin is most likely a result of its agonist action on the relaxing 5-HT<sub>4</sub> receptor as well as on the contracting 5-HT<sub>3</sub> receptor.

It was also deduced from these experiments that compounds having agonist activity to the 5-HT<sub>4</sub> receptor, while having only low or no agonist activity to a 5-HT<sub>3</sub> receptor, therefore are useful as agents for treatment of bronchocontraction disorders.

Thus, the present invention relates to the use of compounds having agonist activity to the 5-HT<sub>4</sub> receptor in the manufacture of a medicament intended for treatment of bronchocontraction disorders, whereby said compounds have the strong bronchorelaxing effect of serotonin but have substantially no contractile effect. As mentioned above, the compounds used according to the present invention have only low or no agonist activity to 5-HT<sub>3</sub> receptors.

In the above mentioned experiments it has also been shown that compounds having antagonist activity to a

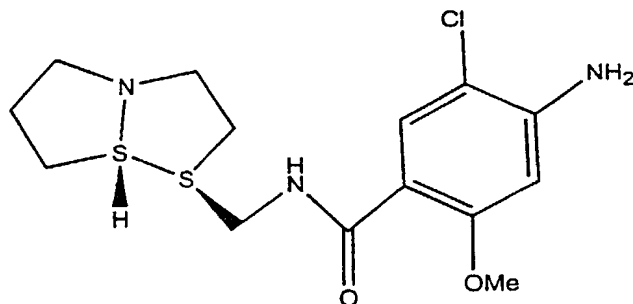


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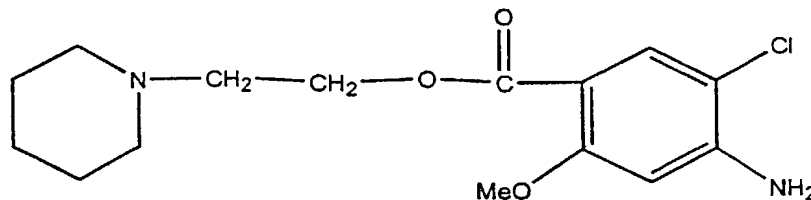
## CLAIMS

1. Compound having agonist activity to a 5-HT<sub>4</sub> receptor, and derivatives and pharmaceutically acceptable salts thereof having agonist activity to the 5-HT<sub>4</sub> receptor for use as a medicament for treatment of disorders involving bronchocontraction.

2. Compound according to claim 1, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide, having the structural formula:



ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic acid-2-(1-piperidiny)ethylester, having the structural formula:

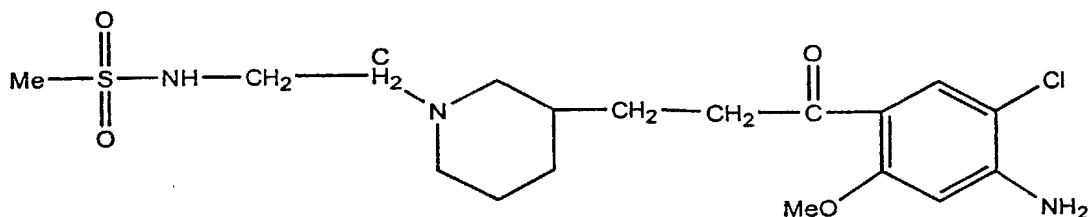


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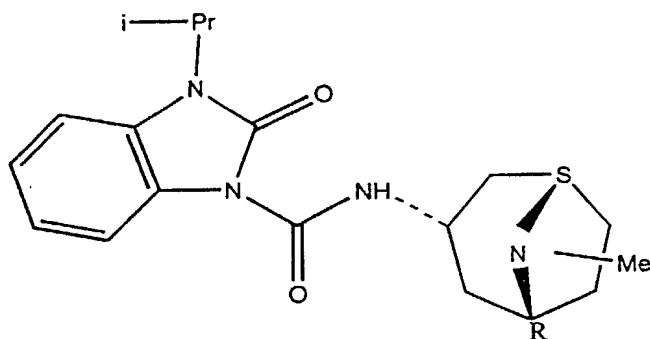
36

RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-methoxyphenyl)-3-oxopropyl]-1-piperidinyl]ethyl]-methanesulfonamide monohydrochloride, having the structural formula:



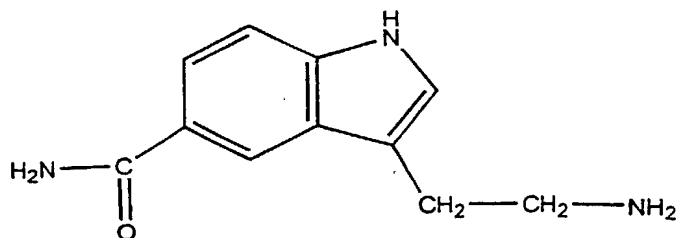
5

BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



10

5-carboxamidotryptamine (5-CT), having the structural formula:



15

ADR932, BIMU 1, BRL 20627, BRL 24682, BRL 24924, Cinita-  
prid, Cisapride, DAU 6215, DAU 6236, 5-HT,

5 5-hydroxy-N,N-dimethyltryptamin, 3-Me-8-OH-DPAT, ML-1035,  
5-metoxytryptamin, Metoclopramide, Mosapride,  
8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin),  
Prucalopride, R 076186, R 093877 (prucalopride), Renza-  
pride, RS 17017, RS 23597-190, RS 56532, RS 57639,

10 RS 67333, RS 67532, RU 28253

SB 204070, SB 205149, SC-52491, SC-49518, SK-951,  
SDZ 216-454, SR59768, TKS159, VB20B7, Y-34959, YM-47813,  
YM-53389, YM-09151, Zacopride, Zelmac (SDZ HTF919; tega-  
serod).

15 3. Compound according to claim 2, wherein said bron-  
chocontraction appears in asthma and disorders related  
thereto, emphysema, chronic bronchitis, chronic obstruc-  
tive pulmonary disease, depression, anorectic or bulimic  
eating disorders, anxiety or various psychotic conditions  
20 including schizophrenia.

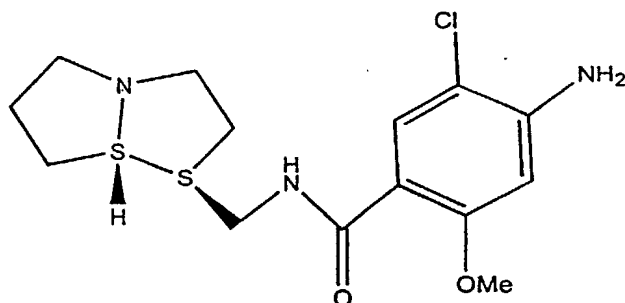
4. Use of one or more compounds according to claims  
1 and 2 having agonist activity to a 5-HT<sub>4</sub> receptor, and  
derivatives and pharmaceutically acceptable salts thereof  
having agonist activity to the 5-HT<sub>4</sub> receptor, in the  
25 manufacture of a medicament for therapeutic or prop-  
hylactic treatment of disorders involving broncho-  
contraction, optionally together with a serotonin uptake  
inhibitor.

5. Use according to claim 4, wherein said one or  
30 more compounds has/have the capacity of reducing the  
pathological bronchocontraction by at least 30%, prefera-  
bly at least 60%, and most preferably at least 90%, and  
wherein said compound(s) is/are chosen from the group  
comprising SC 53116, i.e. 4-amino-5-chloro-N-[[1S, 7aS)-  
35 hexahydro-1H-pyrrolizin-1-yl]methyl]-2-methoxy-benzamide,  
having the structural formula:

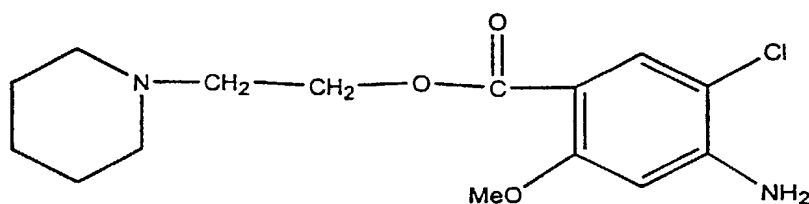
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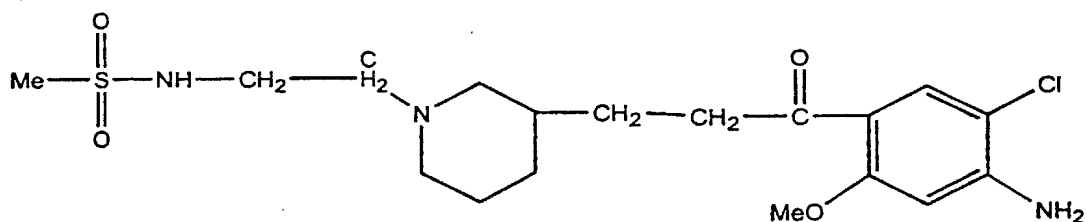
38



ML 10302, i.e. 4-amino-5-chloro-2-methoxy-benzoic  
5 acid-2-(1-piperidiny)ethylester, having the structural  
formula:



10 RS 67506, i.e. N-[2-[4-[3-(4-amino-5-chloro-2-  
methoxyphenyl)-3-oxopropyl]-1-piperidiny]ethyl]-  
methanesulfonamide monohydrochloride, having the struc-  
tural formula:



15

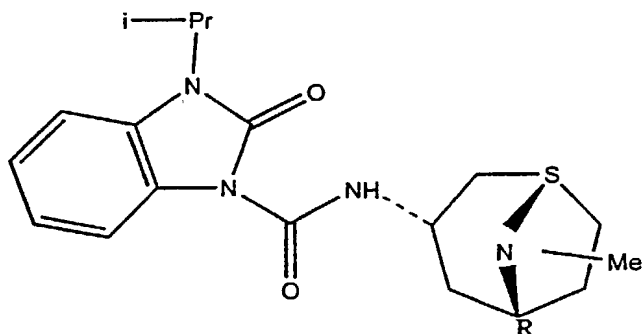


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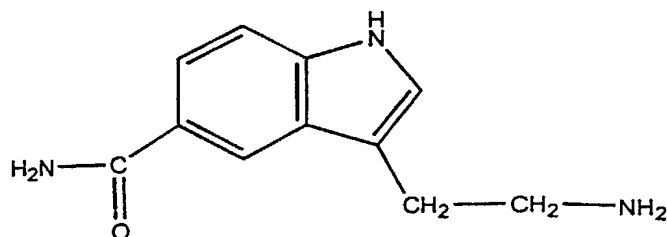
39

BIMU 8, i.e. 2,3-dihydro-N-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-3-(1-methylethyl)-2-oxo-1H-benzimidazole-1-carboxamide monohydrochloride, having the structural formula:



5

5-carboxamidotryptamine (5-CT), having the structural formula:



10

ADR932, BIMU 1, BRL 20627, BRL 24682, BRL 24924, Cinitaprid, Cisapride, DAU 6215, DAU 6236, 5-HT, 5-hydroxy-N,N-dimethyltryptamin, 3-Me-8-OH-DPAT, ML-1035, 5-metoxytryptamin, Metoclopramide, Mosapride, 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), Prucalopride, R 076186, R 093877 (prucalopride), Renzapride, RS 17017, RS 23597-190, RS 56532, RS 57639, RS 67333, RS 67532, RU 28253 SB 204070, SB 205149, SC-52491, SC-49518, SK-951, SDZ 216-454, SR59768, TKS159, VB20B7, Y-34959, YM-47813, YM-53389, YM-09151, Zacopride, Zelmac (SDZ HTF919; tegaserod).

15

20

6. Use according to claims 4 and 5, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

7. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claim 1.

8. Compound having antagonist activity to a 5-HT<sub>3</sub> receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT<sub>3</sub> receptor for use as a medicament for treatment of disorders involving bronchocontraction.

9. Compound according to claim 8, wherein said compound has the capacity of reducing pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound is chosen from the group comprising 4-Ph-N-Me-quipazine, ADR-851, ADR-882, Alosetron, Anpirtoline, Axasetron (=Y 25130), BIMU 1, BMY 33462, BRL 24924, BRL 43694, BRL 46470 A, CF 109203 (=BIM), Chlorpromazine, Cilansetron (=KC 9946), Cisapride, Clozapine, Cyameazine, DAT-582 (=R)AS-5370), Dilalazem, Dolasetron (=MDL 74156), Dolasetron mesilat (=MDL 73147 EF), Droperidol, FK 1052, Fluphenazone, Galanolactone, GK 128, GR 38032 F, GR 65630, Gramisetron (=Kytril=BRL 43694), GR-H, GYK1-48903, ICI 169369, ICS 205-930, Ifonprodil, Iodophenpropit, Itasetron (=DAU 6215), KB-6922, KB-R 6933, KF 17643, KF 18259, L-683877, Litoxetine, LY 278584, McNeil-A-343, MDL 72222, MDL 72699, Metoclopramid, Mirtazapine, Mosapride, N-3389, N-metylquipazin, Ondansetron (=GR 38032 F), Palonosetron, Pancopride, Perphenazine, Prochlorperazine (=Stemetil), Quipazine, QX 222, (R)-zacopride, Ramosetron (=YM 060), Renzapride, RG 12915,

RS-25259, RS 42358-197, RS 56532, RS-056812-198, RS-25259-197, RS-56812, S-apomorphin, SC-53116, SDZ 216-525, SDZ 322, SN-307, Talipexole, Thioperamide, TMB 8, Triti-uoperzine, Trimebutine, Tropisetron (=ICS 205-930=Rifenserin), VA 21 B 7, Way 100289, WAY-100579, WAY-SEC-579, Y 2513, YM 114 (=KAE-393), Zatosetron (=LY 277359), preferably tropanyl-3,5-dimethylbenzoate.

10. Compound according to claim 9, wherein said bronchocontraction appears in asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

11. Use of one or more of the compounds according to claims 8 and 9 and including ketanserin having antagonist activity to a 5-HT<sub>2</sub> receptor, and derivatives and pharmaceutically acceptable salts thereof having antagonist activity to the 5-HT<sub>2</sub> receptor, in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

12. Use according to claim 11, wherein said one or more compounds has the capacity of reducing the pathological bronchocontraction by at least 30%, preferably at least 60%, and most preferably at least 90%, and wherein said compound(s) is/are chosen from the group comprising 4-Ph-N-Me-quipazine, ADR-851, ADR-882, Alosetron, Anpirtoline, Axasetron (=Y 25130), BIMU 1, BMY 33462, BRL 24924, BRL 43694, BRL 46470 A, CF 109203 (=BIM), Chlorpromazine, Cilansetron (=KC 9946), Cisapride, Clozapine, Cyameazine, DAT-582 (=R)AS-5370), Dilalazem, Dolasetron (=MDL 74156), Dolasetron mesilat (=MDL 73147 EF), Droperidol, FK 1052, Fluphenazone, Galanolactone, GK 128, GR 38032 F, GR 65630, Gramisetron (=Kytril=BRL 43694), GR-H, GYK1-48903, ICI 169369, ICS 205-930, Ifonprodil, Iodophenpropit, Itasetron (=DAU 6215), KB-6922, KB-R 6933, KF 17643, KF 18259, L-683877, Litoxetine,

LY 278584, McNeil-A-343, MDL 72222, MDL 72699, Metoclopramid, Mirtazapine, Mosapride, N-3389, N-metylquipazin, Ondansetron (=GR 38032 F), Palonosetron, Pancopride, Perphenazine, Prochlorperazine (=Stemetil), Quipazine,  
5 QX 222, (R)-zacopride, Ramosetron (=YM 060), Renzapride, RG 12915, RS-25259, RS 42358-197, RS 56532, RS-056812-198, RS-25259-197, RS-56812, S-apomorfin, SC-53116, SDZ 216-525, SDZ 322, SN-307, Talipexole, Thioperamide, TMB 8, Tritiuoperzine, Trimebutine, Tropisetron (=ICS 205-930=Rifenserin), VA 21 B 7, Way 100289, WAY-100579, WAY-SEC-579, Y 2513, YM 114 (=KAE-393), Zatosetron (=LY 277359), preferably tropanyl-3,5-dimethylbenzoate.

13. Use of one or more compounds according to claims 11 and 12 in combination, either simultaneously or sequentially, with a compound having agonist activity to the 5-HT<sub>4</sub> receptor in the manufacture of a medicament for therapeutic or prophylactic treatment of disorders involving bronchocontraction, optionally together with a serotonin uptake inhibitor.

14. Use according to claim 13, wherein said compound having agonist activity to the 5-HT<sub>4</sub> receptor is serotonin and derivatives thereof or a compound according to claims 1 and 2.

15. Use according to claims 11-14, wherein said disorder having pathological bronchocontraction is asthma and disorders related thereto, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, depression, anorectic or bulimic eating disorders, anxiety or various psychotic conditions including schizophrenia.

16. A method for treatment of disorders involving bronchocontraction, wherein said method comprises administering to a human or animal patient a therapeutically effective amount of a compound according to claims 11-14.



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| 60/139,633     | 17 June 1999 (17.06.1999)  | US |
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- (71) Applicant (*for all designated States except US*): RESPIRATORIUS AB [SE/SE]; Sölvegatan 41, S-223 70 Lund (SE).
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): SKOGVALL, Staffan [SE/SE]; Flygelvägen 33, S-224 72 Lund (SE).
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(54) Title: RECEPTOR AGONISTS AND ANTAGONISTS



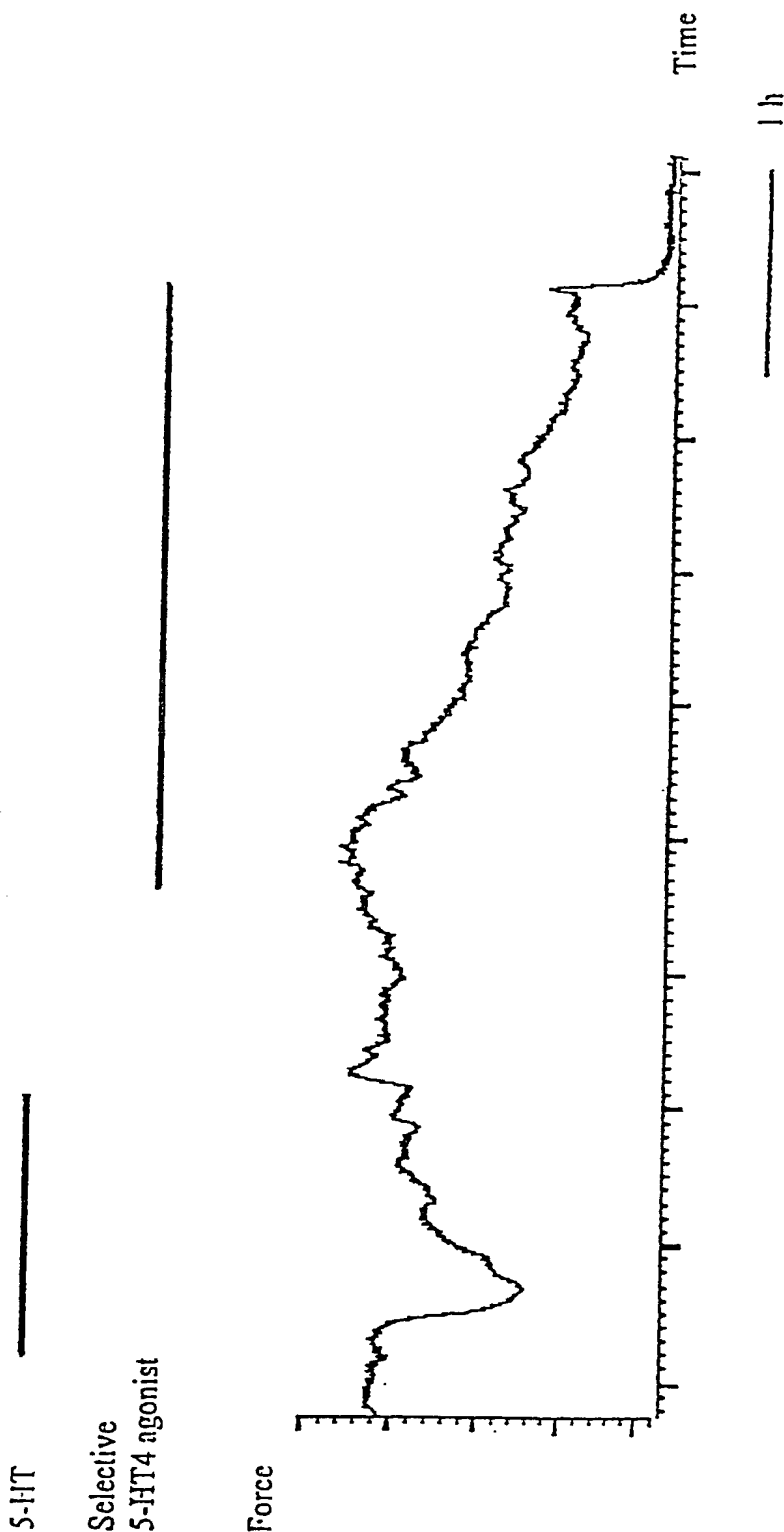
(57) Abstract: The present invention relates to a compound having agonist activity to the 5-HT<sub>4</sub> receptor for use as a medicament and to the use of said compounds in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered. The present invention also relates to a compound having antagonist activity to the 5-HT<sub>3</sub> receptor for use as a medicament and to the use of said compound in the manufacture of a medicament for use in therapeutic or prophylactic treatment of disorders involving bronchocontraction of a human or animal body, as well as methods of treatment, wherein said compounds are administered.

WO 00/76500

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PCT/SE00/01267

Fig 1



This form cannot be amended. Altered  
or changed after it is signed.  
(For use only for inventors who  
understand the English language.)Declaration and Power of Attorney  
United States Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

## RECEPTOR AGONISTS AND ANTAGONISTS

(check one)

☐ is attached hereto.☒ was filed as U.S. Application No. \_\_\_\_\_ on 7 December 2001 and (if applicable) was amended on \_\_\_\_\_.☐ was filed as PCT International Application No. \_\_\_\_\_ on \_\_\_\_\_ and (if applicable) was amended under PCT Article 19 on \_\_\_\_\_.

(I authorize any attorney appointed below to insert information in the preceding blanks.)

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign and PCT application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America listed in this Declaration. I have also identified below any foreign application for patent or inventor's certificate or PCT international application having a filing date before that of the application(s) on which priority is claimed:

Foreign/PCT Application No.	Country	Filing Date	Priority Claimed? (yes/no)
9902251-9	Sweden	15 June 1999	Yes
9902252-7	Sweden	15 June 1999	Yes
PCT/SE00/00819	Sweden	28 April 2000	Yes

I hereby claim the benefit under Title 35, United States Code, § 120 or § 365(c) of any United States application and PCT international application designating the United States of America listed in this Declaration and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, § 112. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

U.S. Application No.	Filing Date	Status (patented/pending/abandoned?)
PCT/SE00/01267	15 June 2000	

I hereby claim priority benefits under Title 35 United States Code § 119(e) of any U.S. provisional application(s) listed below:

U.S. Provisional Application No.	Filing Date
60/139,632	17 June 1999
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I hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Joseph A. DeGrandi (17446), Robert G. Weilacher (20531), Richard G. Young (20628), Michael A. Makuch (32263), Dennis C. Rodgers (32936), Thomas L. Evans (35805), Frank C. Cimino, Jr. (39245), Carolyn Favorito (39183), George A. Metzenthin (P41995), and Steven W. Collier (P42429).

Send all correspondence to Beveridge, DeGrandi, Weilacher &amp; Young, L.L.P., Suite 800, 1850 M Street, N.W., Washington, D.C. 20036. Facsimiles may be sent to (202) 659-1462. Direct all telephone calls to (202) 659-2811.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor: Staffan SKOGVALL  
Residence (city, state, country): Lund, Sweden  
Post office address: Flygelvägen 33, 224 72 LUND, SWEDENCitizenship: SwedishSignature: SSKOGVALL Date: 7 January 2002☐ Additional inventors and/or prior applications are listed in attached Supplemental Sheet(s).